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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,517	02/10/2000	MARCOS DA SILVA FREIRE	3673-2	6833

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	24

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,517	DA SILVA FREIRE ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002 and 24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 3-24-2003 has been entered.

The amendment filed on 8-22-2002 and 3-24-2003 are acknowledged and have been entered. Claims 42-70 have been canceled (8-22-2002 amendment). Claims 71-96 have been added (8-22-2002 amendment). Claim 71 has been amended (3-34-2003). Claims 71-96 are pending and currently under examination.

Claim Rejections Withdrawn

The rejection of claims 42 and 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "acceptable as a substrate for vaccine production" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 42 and 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the term "suitable medium" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 42 and 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "**the** cell culture" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 42 and 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "appropriate period of time" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "harvesting of culture supernatant containing virus with or without addition of stabilizer" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claim 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "optionally, removing cell debris and whole cells from the harvested virus" is withdrawn. Cancellation of said claim has rendered the rejection moot.

The rejection of claims 42 and 58 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "optionally, virus inactivation" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 43 and 59 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase are rendered vague and indefinite by the use of the phrase "submitted to viral infection" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 45 and 61 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "any further passaged" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 49, 50 and 64 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "culture is incubated at steps x, y and z from 12 to 72 (or 144) hours" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 52 and 66 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "acceptable as a component in parenteral products" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 42, 44-45, 49, 51-52, 54-56, 58, 60-61 and 65-69 under 35 U.S.C. 102(b) as being anticipated by Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306) is withdrawn. Cancellation of said claims has rendered the rejection moreover. Moreover, the limitation of 0.2-.0001 infectious units per cell renders the pending free of the cited art.

Claims 42-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306) is withdrawn. Cancellation of said claims has rendered the rejection moreover. Moreover, the limitation of 0.2-.0001 infectious units per cell renders the pending free of the cited art.

Claim Objections

Claim 84 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. Claim 84 reads on all Yellow Fever viruses while its parent claim is limited to attenuated Yellow Fever viruses.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a human vaccine composition comprising propagating Yellow Fever Virus YF17D in chick embryo fibroblasts, does not reasonably provide enablement for methods of producing a human vaccine comprising the propagation of any virus other than YF17D on any cell type other than chick embryo fibroblasts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the applicable factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

The instant claims are drawn to methods of producing a human vaccine comprising the propagation of a virus in permissive cells wherein said cells are initially seeded at a density of less than $2x10^5$ cells/cm^2 and infected with the seed virus at a multiplicity of infection (MOI) of 0.2-0.0001 infectious units per cell. However, the specification provides no guidance as to which virus and cell type other than YF17D and chick embryo fibroblasts could be used in the claimed methods. Moreover, the specification is silent on which viruses are able to infect a given cell type at the claimed MOI. Many viruses (e.g. influenza viruses) cannot be establish stable infections in permissive cells *in vitro* regardless of the MOI used and therefore said cultures are incapable of producing vaccine compositions comprising the infective virus. While the specification provides a single working example in which chick embryo fibroblasts are infected with YF17D, it provides no guidelines for extrapolating said working example for use with any other virus or any other cell type. The specification does not provide guidance as to what the cell density should be at the time of infection nor does it provide any guidance as to how the claimed method needs to be adapted for the varying growth rates of differing cell types encompassed by

the instant claims. Moreover, as pointed out by Applicant, the prior art would lead one of ordinary skill in the art to use higher cell densities and multiplicities of infection than those used in the claimed methods. While the skill level in arts of cell biology and virology is high, one of ordinary skill in the art would not be able to predict which viruses could be used with a given cell type to produce a productive infection resulting in the production of a human vaccine composition utilizing the MOI and cell densities claimed without undue experimentation. Therefore, given the lack of success in the art, the lack of working examples, and the unpredictability of the generation of a productive viral infection in a given cell type, the specification, as filed, is not enabling for methods producing a human vaccine comprising the propagation of any virus other than YF17D on any cell other than chick embryo fibroblasts.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 71 is rendered vague and indefinite by the use of the term "human use vaccines". It is unclear whether Applicant is referring to vaccines for use "in" humans or "by" humans. If the former is true, the term "human vaccine" is suggested.

Claims 71 and 85 are rendered vague and indefinite by the claim language used in step (b) of the claimed method. It is unclear how the claimed cell density of "less than $2x10^5$ cells/cm^2" applies to suspension cultures.

Claims 71 and 85 are rendered vague and indefinite by the claim language used in step (d) of the claimed method. It is unclear how the "removal of the culture medium from the incubated cell culture" results in the formation of a "cell suspension". Moreover, it is unclear how the removal of culture medium from a culture of adherent cells (recited claims read on both adherent and suspension cell cultures) would release said cells from its substrate. Additionally, it should be noted that while step (d) recites the inoculation of the claimed cells with 0.2-0.0001 infectious units per cell, it is unclear what the cell density of the culture is when infected.

Claims 72 and 86 are rendered vague and indefinite by the use of the term "capable of". There is a difference between having a capacity to perform some function and actually performing it. It is unclear whether the production of interferon is meant to be a limitation of the rejected claims.

Claims 75-76 and 89 are rendered vague and indefinite by the use of the term "said density". It is unclear to which culture the recited density is referring to.

Claims 79 and 92 are rendered vague and indefinite by the use of the term "an amino acids". It is unclear whether Applicant is claiming a single amino acid or a multiplicity of amino acids.

Claims 79 and 92 are rendered vague and indefinite by the use of the term "at least two of human albumin, a peptide, an amino acid and a protein". It is unclear what the members constitute the claimed Markush group.

Claim 85 is rendered vague and indefinite by the use of the phrase "preparing a culture of cells which are permissive to Flavivirus and a cell substrate for the production of human vaccines". It is unclear whether the "culture of cells" is the "cell substrate" or whether the "culture of cells" and the "cell substrate" are separate entities.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
May 27, 2003

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